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(54) Title: A METHOD FOR INHIBITING CLOT FORMATION

(57) Abstract

A method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time of greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70 % inhibition of fibrinogen binding to the IIb/IIIa receptor.

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TITLE OF THE INVENTION

A METHOD FOR INHIBITING CLOT FORMATION

BACKGROUND OF THE INVENTION

Platelet activation and aggregation are involved in unstable angina and acute myocardial infarction, in reocclusion following thrombolytic therapy and angioplasty, in transient ischemic attacks and in a variety of other vaso-occlusive disorders. When a blood vessel is damaged either by acute intervention such as angioplasty, or, more chronically, by the pathophysiological processes of atherosclerosis, platelets are activated to adhere to the disrupted surface and to each other. This activation, adherence and aggregation may lead to occlusive thrombus formation in the lumen of the blood vessel.

Antiplatelet therapy has been used in a wide variety of cardiovascular disease states and in conjunction with interventional therapy such as coronary artery or peripheral bypass grafting, cardiac valve replacement, and percutaneous transluminal coronary angioplasty (PTCA). Available drugs, such as aspirin and ticlopidine, have shown efficacy in syndromes involving vascular occlusion, presumably due to sustained inhibition of platelet function. However, the inhibitory effects of aspirin and ticlopidine are dependent upon the agonist which activates the platelet. For example, aspirin is effective in blocking platelet aggregation induced by agonists such as collagen that are dependent upon the cylooxygenase pathway. It is, however, less effective against concentrations of thrombin which can act by cyclooxygenase independent pathways. Likewise, ticlopidine's inhibitory effects can be overcome by combinations of agonists. Thus, an efficacious inhibitor of platelet aggregation that acts independently of the agonist and the pathway activating the platelet could be an important therapeutic advance providing greater efficacy than aspirin or ticlopidine in a broader spectrum of thrombotic events.

GPIIb/IIIa Inhibitors

The final obligatory step in platelet aggregation is the binding of fibrinogen to an activated membrane-bound glycoprotein complex, GP IIb/IIIa ($\alpha_{II}\beta_3$). Platelet activators such as thrombin, collagen, epinephrine or ADP, are generated as an outgrowth of tissue damage. During activation, GP IIb/IIIa undergoes changes in conformation that results in exposure of occult binding sites for fibrinogen. There are six putative recognition sites within fibrinogen for GP IIb/IIIa and thus fibrinogen can potentially act as a hexavalent ligand to crossing GP IIb/IIIa molecules on adjacent platelets. A deficiency in either fibrinogen or GP IIb/IIIa prevents normal platelet aggregation regardless of the agonist used to activate the platelets. Since the binding of fibrinogen to its platelet receptor is an obligatory component of normal aggregation, GP IIb/IIIa is an attractive target for an antithrombotic agent.

Results from clinical trials of GP IIa/IIIa inhibitors support this hypothesis. The monoclonal antibody 7E3, which blocks the GP IIb/IIIa receptor, has been shown to be an effective therapy for the high risk angioplasty population. It is used as an adjunct to percutaneous transluminal coronary angioplasty or atherectomy for the prevention of acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel.

A study reported in The New England Journal of Medicine vol. 330, No. 14, pp. 956-961 (1994) showed a decrease from 12.8% to 8.3% in the combined endpoints of death, non-fatal MI and need for urgent revascularization with fibrinogen receptor blockade. This benefit was at the expense of some additional risk of bleeding, with the need for transfusion increasing from 3% to 6%, and the incidence of patients with decreased hematocrit increasing from 7% to 15%. 7E3 was added to the standard regime of heparin and aspirin thus leaving few hemostatic control mechanisms intact. 7E3 was administered intravenously for 12 hours. The clinical benefits of this drug could be seen at 6 months.

Many other studies have shown that blocking the GPIIb/IIIa receptor will stop platelet aggregation induced by all of the agonists and

thus prevent thrombus formation but leave platelet adhesion relatively intact. The 7E3 monoclonal antibody is described in Coller et al. Ann. NY Acad. Sci. 1991; 614: 193-213; and Coller et al. J. Clin Invest. 1985; 76: 101-108. Others have used agents based on the RGD sequence, including snake venom proteins, small peptides, and peptidomimetics (Cook et al. Drugs of Future 1994; 19: 135-159; and Cox et al. Medicinal Research Reviews 1994; 14: 195-228).

The snake venom proteins, termed disintegrins, have provided important structural information, but their antigenicity has limited their development as therapeutic agents (Cook et al. ibid.; and Cox et al. ibid.). Integrelin is a cyclic peptide that is based on the KGD sequence in the snake venom protein barbourin (Cook et al. ibid.; and Cox et al. ibid.). It inhibits ligand binding to GPIIa/IIIa but has very little effect on ligand binding to $\alpha_v\beta_3$. Among the non-peptide compounds are Ro 44-9883 and MK-383, which are administered intravenously, and are also selective for GPIIb/IIIa (Cook et al. ibid.; and Cox et al. ibid.). Orally active agents include SC54684, which is a prodrug (i.e., it requires biotransformation *in vivo* to its active form) with high oral bioavailability and RO43-8857, GR144053, and DMP728, which are themselves the active inhibitors (Cook et al. ibid.; and Cox et al. ibid.). Literally thousands of other compounds have been synthesized in an attempt to obtain optimal potency, metabolic stability, receptor specificity, and favorable intravascular survival. Despite variations in these compounds, virtually of all of them retain the basic charge relations of the RGD sequence with a positive charge separated from a negative charge by approximately 10-20 Å (Cook et al. ibid.; and Cox et al. ibid.).

Platelet aggregation is profoundly inhibited when increasing concentrations of murine 7E3 or c7E3 Fab are added to platelet-rich plasma *in vitro* or administered in incremental doses to animals or humans *in vivo* (Coller et al. Ann. NY Acad. ibid.; Tcheng et al. ibid.; and Simoons et al. Circulation 1994; 89:596-603). There is an excellent correlation between the percentage of receptors blocked and the inhibition of aggregation, with nearly complete inhibition of aggregation

when 80% or more of the receptors are blocked (Coller et al. Ann. NY Acad. ibid.).

The results of the 7E3 study support the hypothesis that blockade of GPIIb/IIIa receptors is more effective than aspirin in preventing platelet thrombi, even in the presence of heparin. They also support the hypothesis that platelet-dependent thrombi frequently contribute significantly to the development of ischemic complications after PTCA, even when minor mechanical dissections are present.

There are several potential mechanisms by which c7E3 Fab may product a decrease in clinical restenosis. Inhibiting GPIIb/IIIa should lead to fewer platelets in a thrombus that can release PDGF, an agent thought to contribute to restenosis via effects on intimal hyperplasia. In addition, c7E3 Fab decreases platelet thrombus formation, producing less extensive mural thrombus. Since atherosclerosis may undergo rapid progression when the blood vessel incorporates mural thrombus into the wall, a reduction in mural thrombus may translate into decreased progression of the atherosclerotic process. Finally since thrombin itself has been implicated in accelerating intimal hyperplasia (Schwartz J. Clin. Invest. 1993; 91:4), the anticoagulant effect of c7E3 Fab may also contribute to this phenomenon.

7E3 not only blocks the GPIIb/IIIa receptor but also blocks the $\alpha_v\beta_3$ vitronectin receptor, raising the possibility that blockade of this receptor may also contribute to an effect on clinical restenosis. The 7E3 antibody began as an intact murine IgG (Coller et al. J. Clin. Invest. ibid.), but fragments missing the Fc region were used for *in vivo* studies so as to decrease the likelihood of rapid clearance of platelets via an Fc-mediated mechanism (Coller et al. Ann. NY Acad. ibid.). A recombinant chimeric Fab version of 7E3 (c7E3 Fab) containing the mouse variable regions and human constant regions (Tcheng et al. Circulation 1994; 90: 1757-1764) was prepared. All forms of 7E3 inhibit the $\alpha_v\beta_3$ vitronectin receptor as well as GPIIb/IIIa (Coller et al. Blood 1991; 77:75-83; and Coller et al. Ann. NY Acad. ibid.). Since $\alpha_v\beta_3$ is on platelets, endothelial cells, and perhaps smooth muscle cells (Felding-Habermann et al. Curr. Opin. Cell Biol. 1993; 5:864-868), there are many potential

sites of action. Recently Choi *et al.* demonstrated that a peptide that blocks $\alpha_v\beta 3$ prevented intimal hyperplasia after vascular injury in the rat (Choi et al. J. Vasc. Surg. 1994; 19:125-134), and Matsuno *et al.* demonstrated that a peptide that reacts with GPIIIb/IIIa and $\alpha_v\beta 3$ prevents neointima formation in the hamster (Matsuno et al. Circulation 1994; 90:2203-2206). Whether the peptide used by Choi *et al.* also inhibited rat platelet GPIIb/IIIa is not known.

It is known that acute or abrupt closure occurs in 2-8% of patients undergoing percutaneous transluminal coronary angioplasty and accounts for most of the short-term morbidity and mortality associated with the procedure. In about 75% of patients with abrupt closure, it occurs within minutes after percutaneous transluminal coronary angioplasty, when they are still in the catheterization laboratory. In the other 25%, it usually occurs within 24 hours after the procedure (Landau et al. New England Journal of Medicine vol. 330 No. 14 p. 986 (1994)).

We have now found that additionally effective inhibition of platelet aggregation can be obtained by administering, to a patient in need thereof, during a period of time of greater than 24 hours, an amount of a compound which selectively inhibits fibrinogen binding to the GP IIb/IIIa receptor. The effectiveness of this therapy is greater than the effectiveness of therapy only provided only during the first 12 or 24 hours

SUMMARY OF THE INVENTION

The invention is a method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration which provides, during the period of administration, at least about 70% inhibition of fibrinogen binding to the GP IIb/IIIa receptor.

DETAILED DESCRIPTION OF THE INVENTION

The invention is a method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor.

The invention is also a method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time greater than 24 hours, an oral glycoprotein IIb/IIIa receptor antagonist during one portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, and an intravenous glycoprotein IIb/IIIa receptor antagonist during another portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, wherein the oral glycoprotein IIb/IIIa receptor antagonist is orally administered and the intravenous glycoprotein IIb/IIIa receptor antagonist is intravenously administered.

Preferably, the period of time is between about 25 and about 30 hours. More preferably, the period of time is between about 30 and about 36 hours. Even more preferably, the period of time is between about 33 and about 36 hours. Even more preferably, the period of time is between about 36 and about 48 hours.

The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome, comprising administering to the patient, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor.

The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary

ischemic syndrome, comprising administering to the patient, for a period of time greater than 24 hours, an oral glycoprotein IIb/IIIa receptor antagonist during a portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, and an intravenous glycoprotein IIb/IIIa receptor antagonist during another portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, wherein the oral glycoprotein IIb/IIIa receptor antagonist is orally administered and the intravenous glycoprotein IIb/IIIa receptor antagonist is intravenously administered.

Preferably, the period of time is between about 25 and about 30 hours. More preferably, the period of time is between about 30 and about 36 hours. Even more preferably, the period of time is between about 33 and about 36 hours. Even more preferably, the period of time is between about 36 and about 48 hours.

Antagonists for the glycoprotein IIb/IIIa fibrinogen receptor have been described in United States Patents 5,470,849, 5,463,011, 5,455,243, 5,451,578, 5,446,056, 5,441,952, 5,422,249, 5,416,099, 5,405,854, 5,397,791, 5,393,760, 5,389,631, 5,380,713, 5,374,622, 5,358,956, 5,344,783, 5,340,798, 5,338,7235,334,596, 5,321,034, 5,318,899 (e.g. cyclic heptapeptides Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2, Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2, Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,and Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2, wherein Mpr is mercapto propionyl),5,312,923, 5,294,616, 5,292,756, 5,281,585 5,272,158, 5,264,420, 5,260,307, 5,239,113 (e.g. Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate), 5,227,490, 5,206,373, 4,703,036 (e.g. N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide), EP 505 868 (e.g. ((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid) WO 9311152 (e.g. N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)-

carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine), EP 333 356, and WO 9422820. They are described as useful for inhibiting fibrinogen binding and inhibiting clot formation.

Glycoprotein IIb/IIIa receptor antagonists and their pharmaceutically acceptable salts are useful in the present invention. The term "pharmaceutically acceptable salts" means non-toxic salts of the compounds which include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

Pharmaceutically effective amounts of the glycoprotein IIb/IIIa receptor antagonists are suitable for use in the compositions and methods of the present invention. The term "pharmaceutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician.

The methods of the present invention are useful in combination with procedures for treating patients with other anticoagulants (e.g. heparin and warfarin), thrombolytic agents (e.g. streptokinase and tissue plasminogen activator), and platelet antiaggregation agents (e.g. aspirin and dipyridamole).

In accordance with the invention, glycoprotein IIb/IIIa receptor antagonists can be administered to the patient in one oral composition such as a tablet or capsule, in several oral compositions, in one bolus injection, in a continuous intravenous administration, or any combination of oral and intravenous administration, as long as, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor

antagonist is present in the patient's blood in an amount sufficient to achieve a steady state plasma level concentration which provides, during the period of administration, at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor.

Suitable oral compositions include tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Suitable intravenous compositions include bolus or extended infusion. Such oral and intravenous compositions are well known to those of ordinary skill in the pharmaceutical arts.

The active drug may be administered to patients where prevention of thrombosis by inhibition of binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. Such administration is useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy), with stents, and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. The active drugs may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Other applications include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. The methods may also be used to prevent myocardial infarction.

The dosage regimen utilizing the active drug is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of active drug when used for the indicated effects, will range between about 0.005 mg per kg of body weight per day (mg/kg/day) to about 50 mg/kg/day and preferably 0.005-20 mg/kg/day and most preferably 0.005-10 mg/kg/day. Suitable oral tablets contain between 0.5 mg and 5 g, preferably between 0.5 mg and 2 g, most preferably between 0.5 mg and 1g, e.g. 50 mg, 150 mg, 250 mg, or 500 mg. Oral administration may be in one or divided doses of two, three, or four times daily. The dosing objective is to achieve a level of drug for a period greater than 24 hours that is sufficient to provide at least 70% inhibition of fibrinogen binding to GP IIb/IIIa.

Intravenously, the most preferred doses will range from about 0.5 to about 5 mg/kg/minute during a constant rate infusion, to achieve a plasma level concentration during the period of time of administration of between 0.1 ng/ml and 1 μg/ml. The dosing objective is to achieve a level of drug for a period greater than 24 hours that is sufficient to provide at least 70% inhibition of fibrinogen binding to GP IIb/IIIa.

The active drug can be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, distintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-

sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Therapeutic Treatment

The methods for administering the glycoprotein IIb/IIIa receptor antagonist are useful for treating patients where inhibition of human or mammalian platelet aggregation or adhesion is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endaterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interation of platelets with artificial surfaces, leads to platelet aggregation and potential formation of thrombi

and thromboemboli. Methods of the invention may be used to prevent the formation of thrombi and thromboemboli.

The present invention is demonstrated in a study of patients with acute coronary ischemic syndromes who are undergoing early coronary revascularization with percutaneous coronary angioplasty or atherectomy. Because of unstable plaque with thrombus, percutaneous revascularization procedures in these patients carry with them considerable higher morbidity than procedures performed in patients with stable coronary disease. All patients receive heparin (a standard PTCA regimen, weight adjusted in lighter patients) and aspirin. Heparin is discontinued after completion of the procedure and sheaths removed when the heparin-effect has dissipated. GP IIb/IIIa receptor antagonist is continued for a period of time greater than 24 hours. Patients are evaluated at 30 days for acute coronary ischemic syndrome and the need for follow-up intervention associated with acute coronary ischemic syndrome, including coronary artery bypass grafting, repeat percutaneous intervention for acute ischemia, and insertion of a coronary endovascular stent.

EXAMPLE 1

gp IIb/IIIa antagonist treatment (i.v.)

Patients with acute coronary ischemic syndrome received coronary revascularization with angioplasty. Aspirin was administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin was given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units was given during the procedure. The goal was to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin was continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin was required at discharge in a dose of 325 mg per day.

Patients received intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 24-36 hours following angioplasty.

Patients were monitored 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion, and showed reduction in acute coronary ischemic syndrome after 30 days. Reduction was greater than that obtained for patients receiving between 12-36 hours administration.

EXAMPLE 2

gp IIb/IIIa antagonist treatment (i.v.)

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 25-30 hours following angioplasty.

Patients are monitored 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion.

EXAMPLE 3

gp IIb/IIIa antagonist treatment (i.v.)

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 30-36 hours following angioplasty.

Patients are monitored 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion.

EXAMPLE 4

gp IIb/IIIa antagonist treatment (i.v.)

Patients with acute coronary ischemic syndromes received coronary revascularization with angioplasty. Aspirin was administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin was given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units was given during the procedure. The goal was to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin was

continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin was required at discharge in a dose of 325 mg per day.

Patients received intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 33-36 hours following angioplasty.

Patients were monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion, and showed reduction in acute coronary ischemic syndrome after 30 days. Reduction was greater than that obtained for patients receiving between 12-36 hours administration, and greater than that obtained for patients receiving between 24-36 hours of administration.

EXAMPLE 5

gp IIb/IIIa antagonist treatment (i.v. and oral)

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma

level concentration of between 40-60 ng/ml, for 24 hours following angioplasty.

Patients then receive an oral tablet containing 15 mg of the fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid, described in WO 94/18981.

Patients are monitored 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion, and show reduction in acute coronary ischemic syndrome after 30 days.

EXAMPLE 6

Tablet Preparation

Tablets containing 15 mg of the fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid (compound 6-1) are prepared as illustrated below:

Table for doses containing 15 mg of the gp IIb/IIIa receptor antagonist

Ingredient	mg
6-1	15.0
Microcrystalline cellulose	200.0
Modified food corn starch	8.5
Magnesium stearate	1.5

Compound 6-1, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

EXAMPLE 7

Intravenous formulations

An intravenous dosage form of (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (compound 7-1) is prepared as follows:

compound 7-1	0.5-10.0 mg
Sodium Citrate	5-50mg
Citric Acid	1-15mg
Sodium Chloride	1-8mg
Water for Injection (USP)	q.s. to 1 L

Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland, copyright 1994.

EXAMPLE 8

Intravenous formulations

A pharmaceutical composition was prepared at room temperature using compound 7-1, a citrate buffer, and sodium chloride, to obtain a concentration of compound 7-1 of 0.25 mg/ml.

800 grams of water was introduced into a standard pharmaceutical mixing vessel. 0.25 grams of compound 7-1 was dissolved in the water. 2.7 grams sodium citrate and 0.16 grams citric acid were added to obtain a finished citrate concentration of 10 mM. 8 grams of sodium chloride was added. 200 grams of water was then added to achieve the desired final concentrations of ingredients. The resulting aqueous formulation had the following concentrations:

Ingredient	Amount
compound 7-1	0.25 mg/ml
citrate buffer	10 mM
sodium chloride	8 mg/ml

The finished concentrated formulation is stored in a standard USP Type I borosilicate glass container at 30-40 degrees C. Prior to compound administration, the concentrated formulation is diluted in a 4:1 ratio resulting in a finished concentration of 0.05 mg/ml and transferred to an infusion bag.

The following table shows the reduction of risk to the acute coronary ischemic syndrome, including death and nonfatal myocardial infarction, and subsequent follow-up procedures such as coronary artery bypass grafting, repeat percutaneous intervention for acute ischemia, and insertion of a coronary endovascular stent. Patients were evaluated 30 days following initiation of treatment, for patient populations receiving tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756) for periods of time of 12-36 hours, 24-36 hours, and 33-36 hours. Risk reduction was determined by comparing the number patients receiving placebo who experienced acute coronary ischemic syndrome and subsequent follow-up procedures (composite endpoint) with the number of patients receiving tirofiban who experienced acute coronary ischemic syndrome and subsequent follow-up procedures. Higher levels of risk reduction correspond to more effective therapy.

TABLE 1
30 Day Risk Reduction

	Tirofiban administration		
	12-36 hours	24-36 hours	33-36 hours
Composite endpoint	16%	22%	25%

WHAT IS CLAIMED IS:

1. A method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor.

2. A method of claim 1, wherein the glycoprotein IIb/IIIa receptor antagonist is selected from the group consisting of

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide,

((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid,

Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate,

2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid

N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine, and

(2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride.

3. A method for inhibiting platelet aggregation in a patient in need thereof, comprising administering to the patient, for a period of time greater than 24 hours, an oral glycoprotein IIb/IIIa receptor antagonist during one portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, and an intravenous glycoprotein IIb/IIIa receptor antagonist during another portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, wherein the oral glycoprotein IIb/IIIa receptor antagonist is orally administered and the intravenous glycoprotein IIb/IIIa receptor antagonist is intravenously administered.

4. A method of claim 3, wherein the intravenous glycoprotein IIb/IIIa receptor antagonist is selected from the group consisting of

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide,

((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid,

N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine, and

(2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride,

and the oral glycoprotein IIb/IIIa receptor antagonist is 2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid or Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate.

5. A method of claim 1 wherein the period of time is between about 25 and about 30 hours.

6. A method of claim 1 wherein the period of time is between about 30 and about 36 hours.

7. A method of claim 6 wherein the period of time is between about 33 and about 36 hours.

8. A method of claim 1 wherein the period of time is between about 36 and about 48 hours.

9. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome, comprising administering to the patient, for a period of time greater than 24 hours, a glycoprotein IIb/IIIa receptor antagonist in an amount sufficient to achieve a steady state plasma level concentration

which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor.

10. A method of claim 9, wherein the glycoprotein IIb/IIIa receptor antagonist is selected from the group consisting of

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide,

((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid,

Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate,

2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid,

N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine, and

(2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride.

11. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome, comprising administering to the patient, for a period of time greater than 24 hours, an oral glycoprotein IIb/IIIa receptor antagonist during a portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, and an intravenous glycoprotein IIb/IIIa receptor antagonist during another portion of the period of time in an amount sufficient to achieve a steady state plasma level concentration which provides at least about 70% inhibition of fibrinogen binding to the IIb/IIIa receptor, wherein the oral glycoprotein IIb/IIIa receptor antagonist is orally administered and the intravenous glycoprotein IIb/IIIa receptor antagonist is intravenously administered.

12. A method of claim 11, wherein the intravenous glycoprotein IIb/IIIa receptor antagonist is selected from the group consisting of

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide,

((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid,

Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate

N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine, and

(2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride,

and the oral glycoprotein IIb/IIIa receptor antagonist is 2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid or Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate.

13. A method of claim 10 wherein the period of time is between about 25 and about 30 hours.

14. A method of claim 10 wherein the period of time is between about 30 and about 36 hours.

15. A method of claim 10 wherein the period of time is between about 33 and about 36 hours.

16. A method of claim 10 wherein the period of time is between about 36 and about 48 hours.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04631

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44, 31/55, 31/395, 31/415, 31/445, 31/495
US CL :514/212, 218, 331, 352

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/212, 218, 331, 352

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS/USPAT, STN/MEDLINE, HCAPLUS
search terms: GP IIb, glycoprotein IIb, antagonist#, fibrinogen receptor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	KEREIAKES, D.K. Differential Dose-Response to Oral Xemilofiban After Antecedent Intravenous Abciximab. Circulation. 01 September 1996. Volume 94, Number 5, pages 906-910, especially pages 906-907.	1, 3, 9, 11
X ----- Y	US 5,292,756 A (DUGGAN et al.) 08 March 1994, column 7, lines 38-39 and column 10, lines 27-45.	1, 9 ------ 2-8, 10-16
X ---- Y	WO 94/18981 A1 (MERCK & CO., INC.) 01 September 1994, pages 29-32 and 103.	1, 9 ----- 2-8, 10-16
X ----- Y	US 5,470,849 A (CALLAHAN et al.) 28 November 1995, column 20, lines 19-54.	1, 9 ----- 2-8, 10-16

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04631

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHROR, K. Antiplatelet Drugs: A Comparative Review. Drugs. July 1995. Volume 50, Number 1, pages 7-28, especially pages 19-21.	1-16

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